THIOPSEUDOUREA LIGATED PALLADIUM(II) COMPLEXES: SYNTHESIS, CHARACTERIZATION AND APPLICATION AS CATALYSTS FOR C-C COUPLING AND HETEROANNULATION REACTIONS

The thesis deals with the design and development of a new class of phosphine-free palladium catalysts for C–C coupling and heteroannulation reactions. The first chapter contains two sections. Section-A deals with the importance of palladium catalysis and major problems encountered in the conventional homogeneous process. The need for design and development of phosphine-free Pd catalysts for higher order of activity is also discussed in this chapter. Section-B deals with the preparation and characterization of thiopseudourea palladium(II) complexes. Chapter 2 deals with the catalytic activity of thiopseudourea palladium(II) complexes in the Suzuki and Hiyama reactions of aryl halides. Chapter 3 deals with the thiopseudourea palladium(II) complexes catalyzed Heck and Sonogashira reactions of aryl halides. Chapter 4 deals with the synthesis of 2,3-disubstituted indoles by heteroannulation using thiopseudourea Pd(II) complexes as high turnover catalysts for the aryl iodides.

CHAPTER-I:

Section-A: Introduction

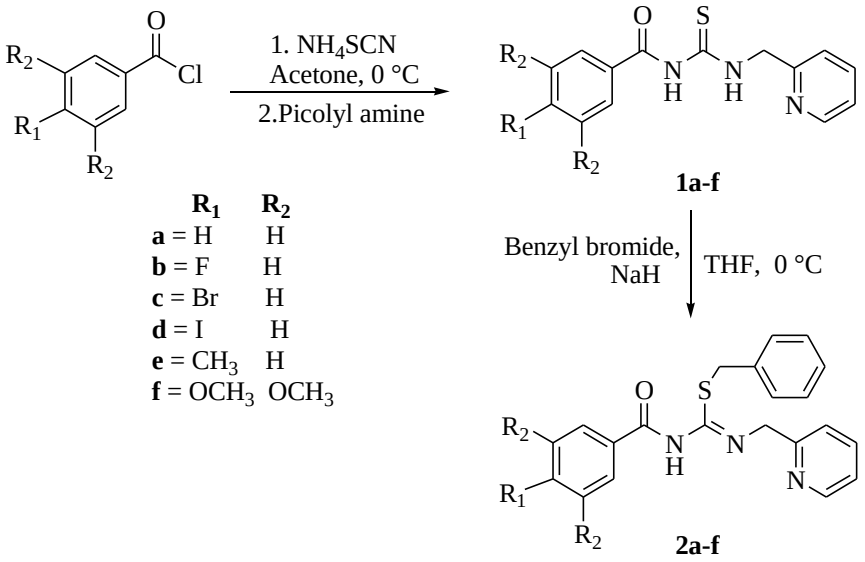
This section introduces the-state-of-the-art practiced in industry and laboratory in the area of palladium catalysis both in homogeneous and heterogeneous conditions. We highlight the importance of ligands for

homogeneous catalysis and the necessity to design and develop the phosphine-free ligands for palladium catalysis. The properties and structures of the ligands like phosphine and phosphine-free (N-heterocyclic carbenes, carbocyclic carbenes) N-donor ligands are discussed to familiarize the ligands used for the development of homogeneous catalysts.

Section-B: Design, Synthesis, and Characterization of Thiopseudourea Ligands and Their Pd(II) Complexes

This section describes the synthesis, characterization of phosphine-free N,N,O-tridentate thiopseudourea ligands and their corresponding Pd(II) complexes. A brief description has been given below.

In contrast to phosphine ligands, the N-donor ligands are stable, inexpensive, easily synthesizable and less toxic. Accordingly, it is highly desirable to develop phosphine-free homogeneous Pd-catalysts for palladium catalyzed coupling reactions. New homogeneous palladium catalysts based on the simple N,N,O-donor ligands were designed and developed (Scheme 1 and 2). The anionic amide (deprotonated amide) ligands were chosen which is expected not only to stabilize the catalytically active palladium particles but also to provide the adequate electron density to the Pd(0) species to facilitate oxidative addition.

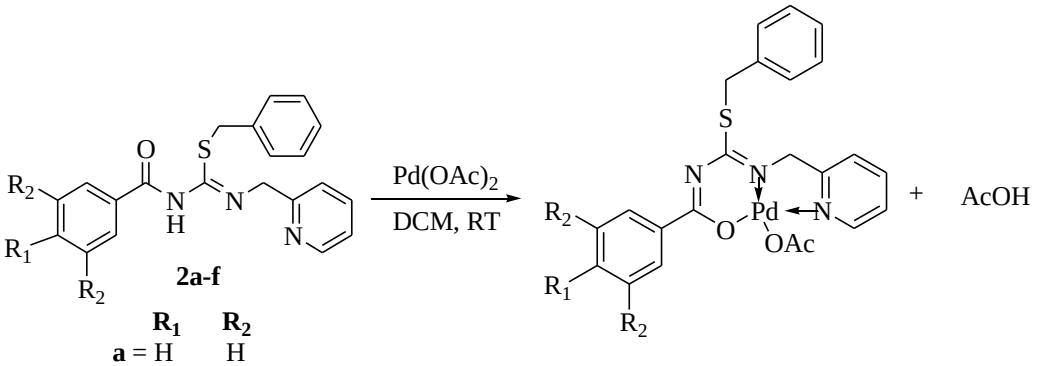


	R_1	R_2
a	H	H
b	F	H
c	Br	H
d	I	H
e	CH_3	H
f	OCH_3	OCH_3

1a-f

2a-f

Scheme 1. Synthesis of thiopseudourea ligands.



2a-f

	R_1	R_2
a	H	H
b	F	H
c	Br	H
d	I	H
e	CH_3	H
f	OCH_3	OCH_3

3a-f

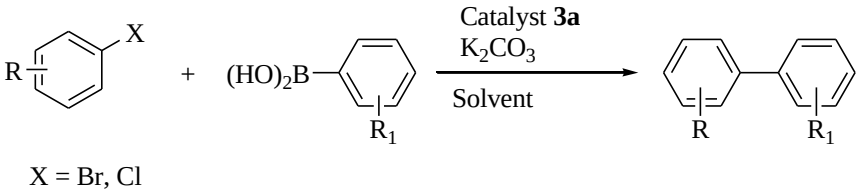
Scheme 2. Synthesis of thiopseudourea-based palladium(II) complexes

CHAPTER-II: Thiopseudourea-Palladium(II) Complexes Catalyzed Suzuki and Hiyama Cross-Coupling Reactions of Aryl Halides

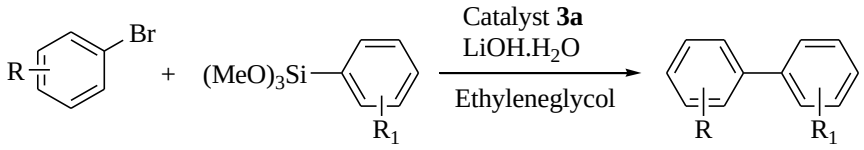
This chapter describes the synthesis of biaryls from Suzuki and Hiyama cross-coupling reactions using thiopseudourea-Pd complexes as catalysts. A brief description has been given below.

The palladium catalyzed Suzuki and Hiyama cross-coupling reactions are the "power tools of contemporary organic synthesis". It consist the arylation of aryl halides, and has found application in natural products synthesis, materials science and bioorganic chemistry. The synthesis of biaryls from chloroarenes is of immense importance, since the C–Cl bond activation contributes to the fundamental understanding of the reactivity of such very stable bonds and they are cheaper and more widely available than their bromide or iodide counterparts. In particular, the activation of aryl chlorides has become an interesting task for Suzuki cross-coupling reaction. Therefore, nowadays there is much interest in the synthesis of catalysts that are able to activate aryl chlorides at lower catalyst loading. Attempts to activate the chloroarenes by strong basic ligands that provide the requisite electron density on palladium to undergo oxidative addition of Pd(0) facilitate the coupling reactions successfully. Phosphine containing ligands and palladacycles thus used to activate the chloroarenes are expensive, toxic and sensitive to air and temperature.

Furthermore, in compare to phosphine ligands, the N-donor ligands are stable, easily synthesizable and less toxic. Consequently, it is highly desirable to develop phosphine-free Pd-catalysts for palladium catalyzed Suzuki reaction of aryl chlorides. New homogeneous palladium catalysts based on the simple N-donor ligands were designed and developed for the Suzuki reaction of chloroarenes. The amide (deprotonated amide) ligands were chosen which is expected not only to stabilize the catalytically active palladium particles but also to provide the adequate electron density to the Pd(0) species to facilitate oxidative addition of chloroarenes. In this chapter, the synthesis of biaryls from Suzuki and Hiyama reactions using thiopseudourea-Pd(II) complexes as catalysts for the of aryl halides was described (Scheme 3 and 4).



Scheme 3. Suzuki reaction of aryl halides catalyzed by palladium complex **3e**.



Scheme 4. Hiyama reaction of aryl bromides catalyzed by palladium complex **3e**.

The noticeable merits of these catalysts are:

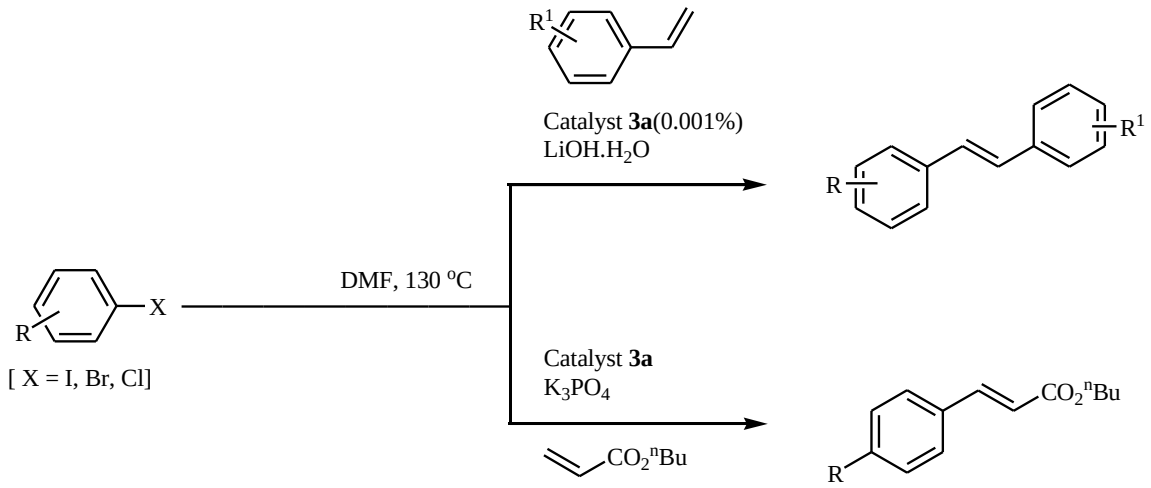
1) Compared to many of the earlier phosphine-free catalysts, these catalysts are air and thermally stable enough and active for the Suzuki reaction of activated aryl chlorides.
2) In case of Hiyama reaction of aryl bromides, additional co-catalysts such as $[NBu_4]Br$ are required to achieve high catalytic activity.

CHAPTER-III: Phosphine-free Thiopseudourea Ligated Pd(II) Complexes Catalyzed Heck and Sonogashira Cross-Coupling Reactions of Aryl Halides

This chapter describes the thiopseudourea ligated Pd(II) complexes catalyzed Heck and Sonogashira cross-coupling reactions of aryl halides. A brief description has been given below.

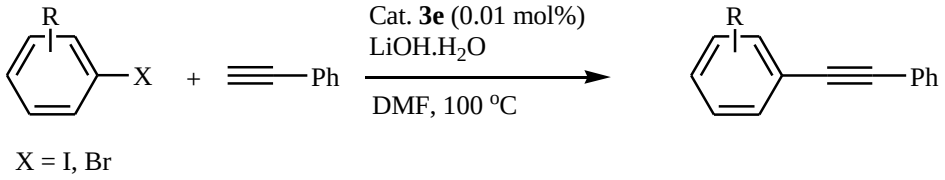
The palladium catalyzed C−C bond formation reactions such as the Heck and Sonogashira cross couplings reactions have found applications in the synthesis of natural products, pharmaceuticals and materials science. The great importance of C−C bond-forming reactions has

encouraged the chemical community to search for highly active and stable palladium catalysts, which should be versatile and efficient. A number of phosphine-free ligands with different donor-functionalities such as N-heterocyclic, carbocyclic and anionic carbocyclic carbenes, oxazolines, schiff bases, pyridines, amines, imidazoles, pyrazoles, hydrazones, selenides, ureas and thioureas have been used for C–C cross coupling reactions. Most of these ligands are mono or bifunctional ligands. Therefore, it was assumed that the design and development of phosphine-free multifunctional ligands using different donor-functionalities may provide stable and well-defined active palladium catalysts.



Scheme 5. Thiopseudourea-Pd(II) complex catalyzed Heck reactions of iodo-, bromo- and chloroarenes.

In this chapter, the successful synthesis of stilbenes, aryl cinnamates and diphenylacetylenes by using thiopseudourea Pd(II) complexes as catalysts for the Heck and Sonogashira reactions was described (Scheme 5 and 6).



Scheme 6. Thiopseudourea-Pd(II) complex catalyzed Sonogashira reactions of iodo and bromoarenes.

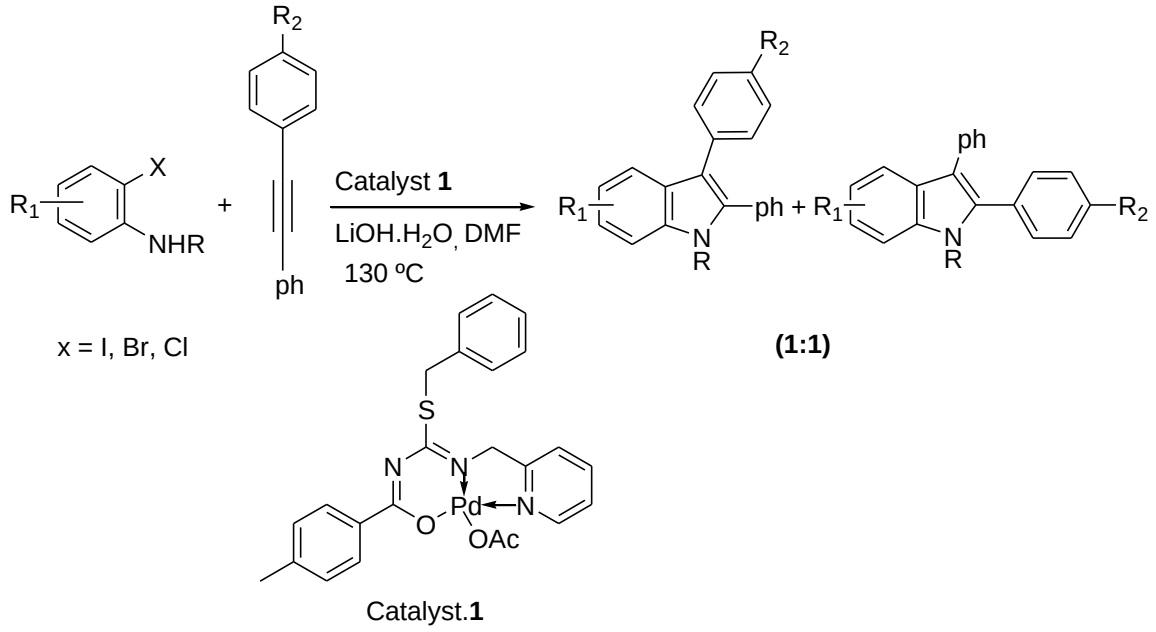
The noticeable merits of these catalysts in C-C bond-forming reactions are:

1) Compared to many of the previous phosphine-free catalysts, these catalysts are air and thermally stable and have long lifetimes.
2) Sonogashira reaction with iodo- and bromoarenes can be performed at 100 °C.
3) Unlike most previously reported systems for C−C cross coupling reactions, additional additives such as [NBu_4]Br or[PPh_4]Cl are not required to achieve high catalytic activity.
4) Catalysts have high turnover numbers with different aryl iodides and aryl bromides in Heck reactions.

CHAPTER-IV: Application of Thiopseudourea ligated Pd(II) Complex as an Efficient Phosphine-free Catalyst for the Larock Indolization

This chapter describes the application of thiopseudourea ligated Pd(II) complexes for Larock indolization and used as high turnover catalysts for the heteroannulation reaction of 2-iodoanilines. A brief description has been given below.

The heteroannulation reaction has become not only one of the most exciting organic transformations for C–C and C–N bonds formation but also a benchmark to estimate the efficiency of a catalytic system. This powerful reaction has received considerable attention due to its functional group tolerance for synthesis of 2,3-disubstituted indoles and its application to a broad range of endeavors, ranging from synthetic organic chemistry to materials science. Therefore, several goals have to be achieved for its industrial application such as the use of inexpensive starting materials, achievement of high TON's with less reactive aryl bromides and aryl chlorides, and the use of stable and inexpensive ligands. In this context, the design of new ligands and their Pd-catalysts that can affect the heteroannulation reaction of less reactive 2-bromo and 2-chloroanilines with both high activity and high efficiency has been a current important topic of research.



Scheme 7. Heteroannulation reactions of 2-haloanilines and N-tosyl-2-haloanilines catalyzed by thiopseudourea-Pd(II) complex.

As the choice of ligand plays a major role in the efficiency of the catalyst, the phosphine ligands are the first choice to catalyze the heteroannulation reactions more actively and efficiently. However, the phosphine ligands are toxic, air-sensitive or quite expensive. Therefore, the development of phosphine-free Pd-catalysts has become another equally important topic of research. In this chapter, the synthesis of 2,3-disubstituted indoles by thiopseudourea palladium(II) complexes bearing N-acylthiopseudourea/pyridyl ligands as N,N,O-donor coordinating sites, together with its performance as high turnover catalysts for the Larock indolization reactions of 2-haloanilines was described (Scheme 7).

The thiopseudourea ligated Pd(II) complexes find their superiority over most of the phosphine-free catalysts with at least one of the following advantages: facile synthesis, thermal stability and structural versatility, easy handling, catalytic performance in air without any additives, achievement of high TON's and presence of N-acylthiopseudourea (RCONHCSNR[1]) hydrogen atom and the TON's with 2-iodoanilines and with hindered 2-bromoanilines, and activation of less reactive 2-chloroanilines.

Significant Achievements:

1) Development of phosphine-free palladium catalysts using N-donor ligands for the Larock indolization reactions
2) The achievement of high turnover numbers for 2-iodoanilines with different diphenyl acetylenes
3) Development of homogeneous phosphine-free palladium catalysts for the Larock indolization of less reactive 2-chloroanilines
4) Application of Thiopseudourea palladium complexes as catalysts for heteroannulation reactions will open a new opportunity for the development of transition metal catalysis under phosphine-free conditions